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Relationships Between Sulcal Asymmetries and Corpus Callosum Size: Gender and Handedness Effects

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Magnetic resonance imaging was used to establish the presence and nature of relationships between sulcal asymmetries and mid-sagittal callosal size in neurologically intact subjects, and to determine the influences of sex and handedness. Against a background of long-standing disputes, effects of gender and handedness on callosal size, shape, and variability were additionally examined. Both positive and negative correlations between sulcal asymmetry and callosal size were observed, with effects influenced by sex and handedness. The direction of relationships, however, were dependent on the regional asymmetry measured and on whether real or absolute values were used to quantify sulcal asymmetries. Callosal measurements showed no significant effects of sex or handedness, although subtle differences in callosal shape were observed in anterior and posterior regions between males and females and surface variability was increased in males. Individual variations in callosal size appear to outrange any detectable divergences in size between groups. Relationships between sulcal asymmetries and callosal size, however, are influenced by both sex and handedness. Whether magnitudes of asymmetry are related to increases or decreases in callosal size appears dependent on the chosen indicators of asymmetry. It is an oversimplification, therefore, to assume a single relationship exists between cerebral asymmetries and callosal connections.

Introduction

Gender differences in callosal morphology have long been in dispute. Sexual dimorphisms reported from post-mortem and magnetic resonance imaging (MRI) studies include (i) larger total or forebrain volume-adjusted size of the corpus callosum (CC) in females (Holloway and DeLacoste, 1986; Johnson *et al.*, 1994; Steinmetz *et al.*, 1995); (ii) larger raw (Witelson, 1989; Steinmetz *et al.*, 1992; Clarke and Zaidel, 1994) or proportional isthmus areas in females (isthmus relative to total CC) (Witelson, 1989); (iii) larger raw or proportional splenial areas in females (DeLacoste-Utamsing and Holloway, 1982; DeLacoste *et al.*, 1986; Holloway and DeLacoste, 1986; Clarke *et al.*, 1989; Davatzikos and Resnick, 1998); (iv) larger posterior callosal regions in males (Denenberg *et al.*, 1991), and (v) shape differences indicating a more bulbous splenium in female compared to male subjects (DeLacoste-Utamsing and Holloway, 1982; Holloway and DeLacoste, 1986; Clarke *et al.*, 1989; Allen *et al.*, 1991). In addition, when comparing angles determined by lines connecting particular points of the CC and other brain regions, gender differences have been observed in the orientation of the CC (Oka *et al.*, 1999). Although these findings suggest that sexual dimorphisms exist in callosal morphology, replications have not been consistent across laboratories, for a review see Bishop and Wahlstein (Bishop and Wahlstein, 1997).

Results are similarly mixed concerning relationships between callosal size and handedness. Post-mortem (Witelson, 1985, 1989; Witelson and Goldsmith, 1991) as well as *in vivo* studies (Denenberg *et al.*, 1991; Habib *et al.*, 1991) have shown smaller

callosal size in right compared with left handers and ambidextrous individuals. Gender by handedness interactions, as reported by Denenberg *et al.* (Denenberg *et al.*, 1991) and Habib *et al.* (Habib *et al.*, 1991) also appear present where larger callosal anterior midbody regions in right-handed females, left-handed and non-consistent right-handed males as well as larger posterior midbody regions in consistent right-handed females have been documented. Several studies, however, have failed to detect differences in callosal morphology in association with hand preference (Kertesz *et al.*, 1987; Steinmetz *et al.*, 1992, 1995). A number of explanations may account for discrepancies in results between laboratories including the composition of brains examined, and differences in the methods employed for measuring callosal subregions. The largest source of discrepancy, however, is likely attributable to the failure of most prior studies to take total brain weight or volume into account.

Cerebral lateralization, in addition to sex and handedness, may also influence callosal morphology. For example, if processing resources were shared between the hemispheres, this would lead to increased requirements for hemispheric communication, and thus a positive correlation between functional lateralization and callosal size may be observed. However, e.g. Hines and colleagues (Hines *et al.*, 1992) observed a negative correlation between language lateralization and the size of the callosal splenium. This finding lends support to the hypothesis that when the processing takes place solely or dominantly in a single hemisphere, there may be less need for interhemispheric information exchange. This could be related to a decreased callosal size, and therefore a negative correlation may exist between functional lateralization and callosal size. In contrast, others view callosal size as an indicator for hemispheric isolation: the larger the CC, the greater the interhemispheric inhibition, and the more isolated the hemispheres in function (Clarke *et al.*, 1993; Clarke and Zaidel, 1994; Hellige *et al.*, 1998). Additionally, Cook (Cook, 1984a,b,c) proposed a mechanism for interhemispheric communication in which the pattern of cortical activation in one hemisphere results in ipsilateral surround inhibition and contralateral homotopic inhibition. Therefore, if the CC is assumed to have an inhibitory function, and if we suppose a stronger inhibition in asymmetric brains, we might expect to find positive relationships between CC size and asymmetry measures.

Although functional lateralization has been hypothesized to be linked with the degree of structural asymmetry (Foundas *et al.*, 1994, 1996; Jancke *et al.*, 1994; Schlaug *et al.*, 1995; Steinmetz, 1996; Amunts *et al.*, 1996, 2000), surprisingly few human studies have examined the relationships between structural asymmetries and callosal morphology directly. Based on negative correlations revealed between the density of callosal projections and volumetric asymmetry in the cortex of the rat, Rosen and colleagues (Rosen *et al.*, 1989, 1990) and Galaburda *et*

al. (Galaburda *et al.*, 1990) have proposed that an inverse relationship exists between the magnitude of anatomical cerebral asymmetry and the extent of commissural connections between the relevant cortical areas. Findings from some investigations of the human brain further suggest that such an inverse relationship exists. Specifically Aboitiz *et al.* (Aboitiz *et al.*, 1992b,c) and Zaidel *et al.* (Zaidel *et al.*, 1995) analyzed statistical associations between the degree of asymmetry in perisylvian regions [Sylvian fissure (SF) curved length, planum temporale (PT) area and depth] and commissural connections (indexed by the regional number of callosal fibers or by regional callosal size) in post-mortem brains. In these investigations, a negative correlation was observed between perisylvian asymmetries and the total numbers of fibers in the isthmus of males, and in the anterior splenium of females (Aboitiz *et al.*, 1992b). Negative correlations between SF and PT asymmetries and the size of the callosal isthmus were observed in males but not in females (Aboitiz *et al.*, 1992c) and between PT asymmetry and the number of small diameter fibers in the isthmus of the CC, again only in male brains (Zaidel *et al.*, 1995). Only one study, to our knowledge, has examined these relationships using *in vivo* imaging data, where links between midsagittal callosal area and overall cerebral asymmetry (measured from one matched sagittal brain slice in each hemisphere) were assessed (Dorion *et al.*, 2000). Results showed a negative correlation between cerebral asymmetry and total callosal size in male subjects. Although methods differ considerably, all of these studies suggest a sex-dependent decrease in callosal size and fiber number with increasing cerebral asymmetry. However, not all of these investigations employed brain size corrections to control for differences in the magnitude of asymmetry between genders. Importantly, males are well known to possess larger brains and are thus expected to exhibit larger hemispheric differences. Furthermore, it is possible that post-mortem measurements may be compromised by a non-uniform shrinkage of the CC. Finally, measurements obtained from one brain slice in each hemisphere may be a less precise index of asymmetry and sensitive to the orientation of each brain volume.

In the present study, our first goal was to confirm the presence, and establish the nature of relationships between callosal size and well documented indices of sulcal asymmetries (Thompson *et al.*, 2000; Blanton *et al.*, 2001; Narr *et al.*, 2001; Sowell *et al.*, 2002a). Sulcal asymmetry was defined as the interhemispheric difference in the surface location of a defined single point representing the anterior, posterior, superior or inferior end of a sulcus. Points rather than linear measures (although highly correlated) were used as asymmetry measures as based on previous analyses showing that points from the sulcal extremes are slightly better predictors of cerebral asymmetry than hemispheric differences in sulcal lengths or heights (Narr *et al.*, 2001). For example, measures of SF posterior extrema are highly correlated with SF horizontal length, and measures of SF superior extrema are highly correlated with measures of SF height. Sulcal extreme points represent a proxy to the positions and extent of the tissue, encompassed by the respective sulci. For example, the posterior extent of the superior temporal sulcus ascending branch represents the angular gyrus. The termination of this sulcus is in the bend of the angular gyrus. It represents a single point that is sufficiently stable to serve as a proxy for the position of the angular gyrus. Thus, hemispheric differences in the location of sulcal extrema express the positional or size dependent asymmetry of a particular brain region. The degree of structural asymmetry has been hypothesized to be linked with functional asymmetry,

while both structural and functional asymmetry are proposed to be associated with the degree of interhemispheric communication or callosal connectivity. However, given that there is a disagreement in the existing literature concerning whether increased callosal connectivity is associated with more versus less lateralization and that existing empirical data are relatively sparse, our hypotheses were two-tailed.

Asymmetry measures included sulcal measurements from frontal, temporal and parietal regions. Measures were specifically chosen from posterior brain regions established as asymmetric in normal individuals and as important for language processing. Finally, although less widely documented as asymmetric, we included sulcal measures surrounding anterior language regions from each hemisphere. Anatomical relationships were investigated between sulcal asymmetries and total CC area as well subareas of discrete callosal vertical partitions. To our knowledge, it is the first 3-D *in vivo* study examining associations between callosal sizes and cerebral asymmetry using a refined set of sulcal extrema measures. Previous studies have used only a single SF and PT asymmetry measurement or an overall hemispheric asymmetry measure as based on a single sagittal brain slice in each hemisphere.

As a second goal of this study we set out to examine whether relationships between sulcal asymmetries and callosal size were different in male and female subjects and between right- and left-handed individuals, given that gender, handedness, and their interactions appear to contribute to changes in callosal morphology. Furthermore, in light of above-mentioned controversies concerning the influences of sex and handedness on callosal morphology, we examined differences in callosal areas between groups defined by biological sex and handedness in a large and age-matched sample to help clarify previous findings. Anatomical surface based mesh modeling methods (Thompson *et al.*, 1996a,b, 1997; Narr *et al.*, 2000, 2002) were further used to characterize average shape and detailed surface variability differences between groups.

Materials and Methods

Subjects

Subjects without any neurological, psychological or pathological impairment ($n = 59$) from the International Consortium for Brain Mapping (ICBM) database of normal adults were included for study. Groups were matched for biological sex, handedness and imaging site (McConnell Brain Imaging Center at the Montreal Neurological Institute (MNI) of McGill University, the Research Imaging Center (RIC) at the University of Texas Health Science Center at San Antonio, and the Division of Brain Mapping at the University of California, Los Angeles (UCLA) School of Medicine). Handedness was quantified with a Laterality Quotient (LQ) using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). LQs that approach -100 represent left-dominant subjects and those that approach 100 represent right-dominant subjects. Only subjects with LQs that represent largely left-dominance and largely right-dominance were included (left handers mean LQ = 78.5, SD = 23.8; right handers mean LQ = 98, SD = 6.1). Cross-dominance was minimized to eliminate a potential confound in the study. UCLA's ICBM database contained only four qualified left-handed females accounting for one less female left-handed subject from this site. Overall, there were 15 male right-handed subjects (mean age = 23.3 years, SD = 3.9), 15 male left-handed subjects (mean age = 25.3 years, SD = 6.2), 15 female right-handed subjects (mean age = 23.3 years, SD = 3.9), and 14 female left-handed subjects (mean age = 25.4 years, SD = 5.7). All subjects gave informed consent according to institutional guidelines.

MRI Acquisition

T_1 -weighted spoiled grass (SPGR) whole brain MRI scans were obtained for each subject (MNI: 1.5 T Siemens, $176 \times 256 \times 256$ $1 \times 1 \times 1$ mm

voxels; RIC: 2 T Elscint, $190 \times 256 \times 256$ $1 \times 1 \times 1$ mm voxels; UCLA: 3 T General Electric, $124 \times 256 \times 256$ $1.2 \times 1 \times 1$ mm voxels).

Image Preprocessing

Sulcal Asymmetry Measures

To obtain sulcal asymmetry measures, image volumes passed through a number of preprocessing steps. First, image volumes were corrected for signal intensity inhomogeneities (Zijdenbos *et al.*, 1994; Zijdenbos and Dawant, 1994; Sled *et al.*, 1998), and transformed into ICBM 305 stereotaxic space using an automatic nine-parameter linear transformation (Woods *et al.*, 1998). Using signal intensity information a spherical mesh surface was created and continuously deformed to fit a threshold intensity value which best differentiates extra-cortical cerebrospinal fluid from underlying cortical gray matter (MacDonald *et al.*, 1994). The resulting 3-D cortical surface models from each subject were used to manually outline primary cortical surface sulci and fissures in each hemisphere by two raters blind to group status (Thompson *et al.*, 2000; Sowell *et al.*, 2002a,b). Images volumes in coronal, axial and sagittal planes were available simultaneously to aid decisions when the brain anatomy was ambiguous. Detailed anatomic protocols for delineating cortical anatomy are available at <http://www.loni.ucla.edu/NCRR/Protocols/SulcalAnatomy.html> and have been previously validated (Blanton *et al.*, 2001; Narr *et al.*, 2001; Sowell *et al.*, 2002a). The reliability for the sulcal delineation procedure was established with an inter-rater error of <2 mm for all sulci (right hemisphere only) of six different randomly selected brains (Sowell *et al.*, 2002a). After outlining the cortical surface sulci, we identified the surface locations of defined points representing sulcal openings and/or termination points from anterior, posterior, superior or inferior sulcal extrema [minima or maxima in z (horizontal) or y (vertical) dimensions]. Sulcal measures reflect distances as measured from the anterior commissure, which was defined as the origin in each brain volume (0,0,0 in x,y,z coordinates).

For the present study, only sulcal parameters exhibiting highly significant hemispheric asymmetries in posterior temporo-parietal regions as identified in both normal and diseased populations (Narr *et al.*, 2001) were used to assess associations with vertically partitioned

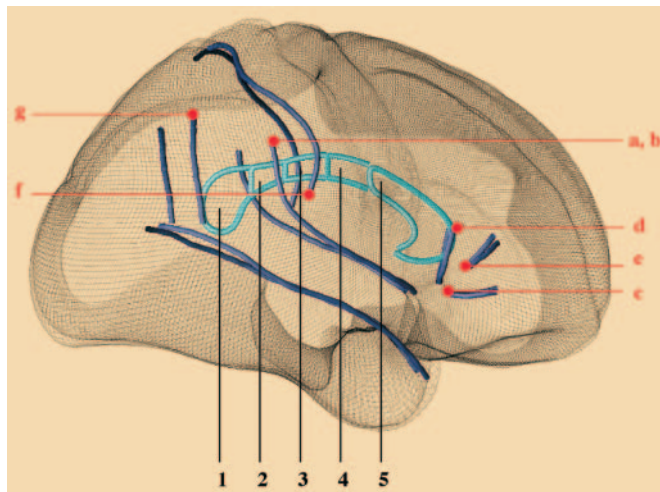


Figure 1. Three-dimensional model of the cerebral cortex showing sulcal landmarks and callosal area measures. Structures are visualized as follows: (1) splenium, (2) isthmus, (3) posterior midbody, (4) anterior midbody, (5) anterior third, (a) posterior extrema of the SF, (b) superior extrema of the SF, (c) SF inferior extrema of the anterior horizontal ramus, (d) SF anterior extrema of the anterior vertical ramus, (e) sulcus triangularis inferior extrema, (f) post central sulcus anterior extrema, and (g) posterior extrema of the superior temporal sulcus ascending branch. Although the SF posterior and superior extrema seem to represent the same extrema in Figure 1, the posterior ending of the SF is represented by an extrema in the vertical dimension, while the superior ending of the SF is represented by a different extrema in the horizontal dimension.

midsagittal areas of the CC. These measures were also chosen because they delimit posterior brain regions established as important for language processing. Measures included the posterior and superior extrema of the SF, the anterior extrema of the post central sulcus and the posterior extrema of the superior temporal sulcus ascending branch. Additionally, we examined relationships between callosal areas and sulcal parameters delimiting anterior language regions. These measures included the SF inferior extrema of the anterior horizontal ramus, the SF anterior extrema of the anterior vertical ramus and the sulcus triangularis inferior extrema (Fig. 1).

Callosal Measures

One rater, blind to gender and handedness, delineated the CC in the midsagittal sections of native brain volumes after correcting image volumes for signal intensity inhomogeneities (Zijdenbos *et al.*, 1994; Zijdenbos and Dawant, 1994; Sled *et al.*, 1998) using a 3-D visualization program (Woods, 2001). Midsagittal brain sections were defined by identifying the interhemispheric fissure in the coronal and sagittal planes and confirmed by the presence of the falx cerebri. For inter-rater reliability, the CC from six different randomly selected brains were contoured by two independent investigators. The intraclass correlation coefficient obtained for total CC area was $r = 0.99$. The midsagittal callosal renderings in native space were reoriented to maximize callosal length and divided into five vertical partitions representing the (i) splenium, (ii) isthmus, (iii) posterior midbody, (iv) anterior midbody and (v) anterior third (Fig. 2). This parcellation scheme was devised by Witelson (Witelson, 1989) based on electron microscopic study of callosal fibers in the macaque, and validated by Aboitiz *et al.* (Aboitiz *et al.*, 1992a) in post-mortem analyses as well as by Clarke and Zaidel *et al.* (Zaidel *et al.*, 1994) in *in vivo* analyses.

Midsagittal area measures were acquired in mm^2 for each segment as well as for the entire CC. In order to clarify findings concerning gender specific shape differences of splenial area (DeLacoste-Utamsing and Holloway, 1982; Holloway and DeLacoste, 1986; Clarke *et al.*, 1989; Allen *et al.*, 1991), the splenial extent in the y -dimension (length) was measured in mm.

Finally, to obtain maps of average callosal anatomy and detailed surface variability information, callosal surfaces were delineated in ICBM 305 stereotaxic space as detailed above, and surface-based anatomical

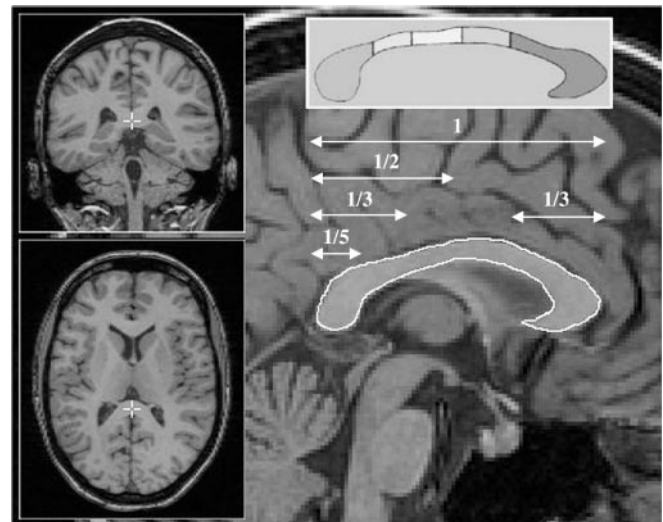


Figure 2. Delineation and partitioning of the midsagittal corpus callosum in T_1 -weighted MR images. The CC was traced in the most medial brain slices. The partitioning scheme adapted from Witelson (Witelson, 1989), Aboitiz and colleagues (Aboitiz *et al.*, 1992a), and Clarke and Zaidel (Clarke and Zaidel, 1994) was employed to divide callosal areas into the splenium, representing the posterior fifth of callosal area, the isthmus representing two-fifteenths, the posterior midbody and anterior midbody, both representing one-sixth of callosal area; and the anterior third as shown.

mesh modeling methods were applied (Thompson *et al.*, 1996a,b, 1997). For these procedures surface points making up each callosal outline were made spatially uniform in 3-D. Homologous callosal surface points were then matched between subjects within groups defined by biological sex and/or handedness in all three dimensions. The mean and root mean square distance between these sets of points were calculated to provide maps of average callosal shape and variability on a point-by-point basis across the entire surface in standard ICBM 305 space.

Brain Volume

Brain volume was estimated from the cortical surface models described above in raw scanner space. That is, the 3-D cortical surface models were mapped back onto each image volume and masks of brain tissue were obtained. Any small errors in the masks were corrected manually. All extra-cerebral tissue was then removed from the image volumes based on the brain mask to provide measures of intracranial brain volume that included all tissue types (gray matter, white matter, and cerebrospinal fluid) but that excluded the cerebellum.

Statistical Analysis

Corpus Callosum Morphology and the Influence of Gender and Handedness

In order to control for the influence of total brain volume on midsagittal callosal (sub)areas and splenial length, the CC measures obtained in raw scanner space were residualized by the square of the cubed root (area measures) or by the cubed root (length) of each individual brain volume. For comparisons between groups defined by biological sex and handedness we used multivariate analyses of variance, which were followed by univariate analyses when appropriate. Morphometric variables were used as repeated measures in a two (Gender) by two (Handedness) design and included the residualized areas of (i) the total callosum, (ii) the anterior third, (iii) the anterior midbody, (iv) the posterior midbody, (v) the isthmus, (vi) the splenium and (vii) the splenial length as dependent measures. Although the primary objective of this study was to examine differences in callosal size after controlling for individual differences in brain volume, we also performed analyses without taking brain volume into account in order to compare our findings with others in the literature. Using Bonferroni corrections for these tests was considered overly conservative given that MANOVAs already protect against inflated Type I error (Tabachnick and Fidel, 1996). Finally, differences in total brain volume between groups defined by sex and handedness were examined using standard analyses of variance.

Relationships Between Sulcal Asymmetry and Callosal Area Measures

The term 'sulcal asymmetry' refers to the interhemispheric difference of the location of defined points representing sulcal extrema. Asymmetry coefficients for sulcal extrema were calculated by subtracting right from left hemisphere sulcal measures (L-R). As described previously, sulcal measures were obtained after brain volumes had been transformed into average 305 stereotaxic space, thus already controlling for brain size contributions to increases in cortical asymmetry indices as may occur between genders. Given that brain size differences for sulcal parameters were controlled, it was therefore unnecessary to divide asymmetry measures by the sum of left and right hemispheric values to obtain relative

asymmetry measures. Pearson's correlation coefficients were used to establish linkages between residual callosal areas and sulcal asymmetry measures.

In previous studies, both absolute and directional asymmetry measures have been used to examine relationships between hemispheric asymmetries and callosal size. To establish which of these approaches was more appropriate, we calculated the exact probability that distributions for asymmetry coefficients from each sulcal measure could have arisen by chance by modeling the data as a binomial distribution using equal probabilities that right or left measures were more extreme. For measures revealing significant deviations ($P \leq 0.01$) from this directionally unbiased binomial distribution, that is when measures indicated a significant leftward or rightward shift in sulcal asymmetry, we used real values (positive and negative) to examine if leftward or rightward asymmetries influence the direction of the correlations with callosal areas. For measures indicating no significant sulcal asymmetry shift in either direction, absolute values were used for correlations between callosal areas and asymmetry. The results of these tests are presented in the Results section.

To determine the appropriate Bonferroni correction for having performing multiple correlations between sulcal asymmetry measures and callosal area measurements, we examined the relationships between different sulcal asymmetry indices (separately for absolute value and real value asymmetry indices as established above). Measures that were highly correlated were counted as a single measure for the purpose of Bonferroni correction. Correlations between the dependent measures are provided in the Results section. Significance was determined with a two-tailed probability value of alpha less than 0.05.

Results

Corpus Callosum Morphology and the Influence of Gender and Handedness

Table 1 shows means and standard deviations for total brain volume and callosal measures obtained in raw scanner space for the overall sample and for groups defined by biological sex and handedness.

Total brain volumes obtained from the present sample of young adults are somewhat smaller in comparison to other post-mortem and *in vivo* measures as found in the literature given that the cerebellum was excluded when estimating the brain volume. As expected, males possessed significantly larger brain volumes compared with females ($P \leq 0.001$; $F = 29.34$). Callosal (sub)regions revealed no significant differences between males and females both before and after brain size correction. Size and shape differences of callosal surface anatomy may be visualized between males and females in Figure 3 where surface averages are superimposed from each group in standard 305 stereotaxic space. As illustrated, differences between males and females appear situated predominantly in anterior and posterior callosal regions, and a subtle shape difference can be identified in the splenial region (although the gender difference of the splenial

Table 1

Means (and SD) of brain volume and areas of the corpus callosum

	Total <i>n</i>	Male	Female	Left-handed	Right-handed
Brain volume (l)	1.12 (0.13)	1.19 (0.12)	1.05 (0.10)	1.12 (0.13)	1.12 (0.12)
Total CC (mm ²)	654.54 (86.92)	676.96 (93.77)	631.34 (73.82)	653.45 (95.32)	655.58 (79.60)
Anterior third (mm ²)	251.89 (40.78)	261.34 (43.60)	242.12 (35.80)	249.98 (43.94)	253.74 (38.15)
Anterior midbody (mm ²)	77.75 (12.45)	78.75 (14.48)	76.71 (10.09)	77.70 (13.71)	77.79 (11.34)
Posterior midbody (mm ²)	70.68 (11.51)	71.63 (10.86)	69.70 (12.26)	70.57 (13.44)	70.79 (9.52)
Isthmus (mm ²)	59.01 (12.33)	62.34 (13.06)	55.57 (10.67)	60.94 (11.31)	57.14 (13.15)
Splenium (mm ²)	190.04 (28.68)	197.60 (31.54)	182.21 (23.43)	189.20 (28.66)	190.85 (29.17)
Splenium Length (mm)	18.79 (2.50)	19.92 (2.71)	17.62 (1.60)	18.90 (2.34)	18.69 (2.68)

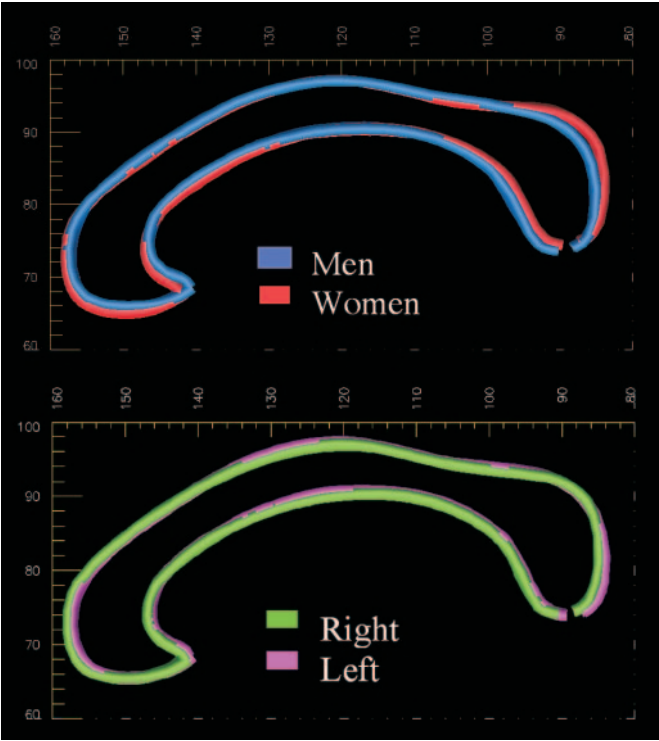


Figure 3. Callosal surface averages mapped in groups defined by sex and handedness. The average parametric midsagittal mesh models of the CC in the average ICBM 305 stereotaxic space are shown in different colors to illustrate differences between groups with females ($n = 29$) shown in red, males ($n = 30$) in blue, right-handed subjects ($n = 30$) in green, and left-handed subjects ($n = 29$) in pink. The anterior third is on the left and the splenium on the right.

length was not identified as significant in the omnibus analysis described above).

Total brain volume and callosal regions did not differ significantly between left- and right-handed subjects before and after brain size correction. Furthermore, no significant interactions between gender and handedness were observed for any of these measures. Superimposed surface maps of the CC averaged within right and left handers in 305 space are consistent with statistical analyses where surface averages are almost perfectly aligned, although small differences may exist in splenial regions (Fig. 3).

Corpus Callosum Surface Variability

The surface variability of the CC, shown in Figure 4, appears larger in males than in females for the overall sample and in groups defined by hand preference and sex. In contrast, similar variabilities exist in the CC when groups are divided by hand preference only. In callosal subregions, higher variabilities are seen in all groups in the anterior and posterior borders of the splenium and the anterior third of the CC. The smallest inter-individual differences in females are present in the inferior and superior borders of the isthmus and the posterior midbody as well as in the inferior surface of the CC anterior third. The least variability in males, left handers and right handers can be seen in the inferior surface of the CC anterior third.

Relationships Between Sulcal Asymmetry and Callosal Area Measures

Results from exact binomial modeling revealed significant ($P \leq 0.01$) leftward or rightward asymmetries for the following

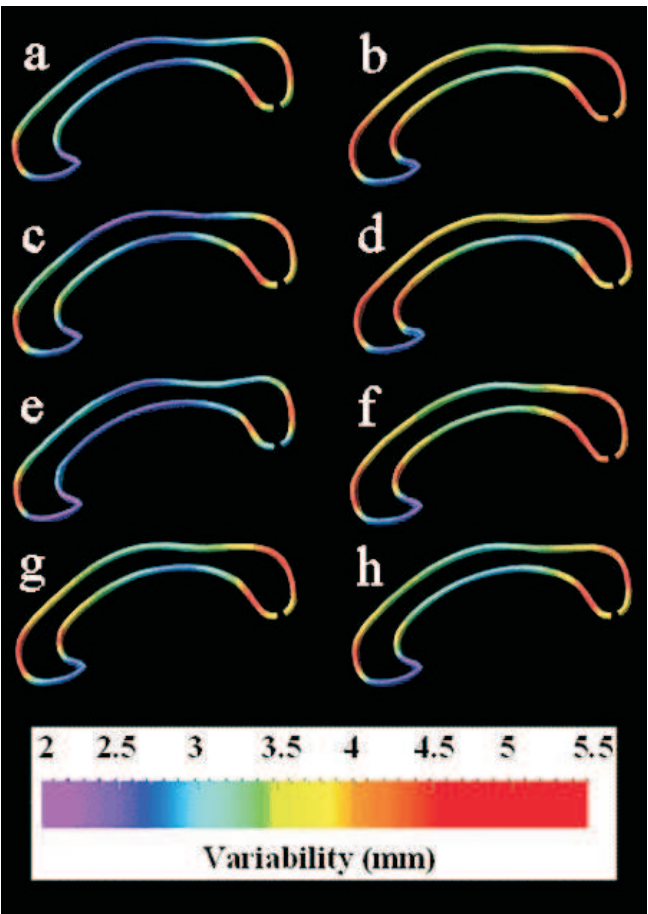


Figure 4. Callosal surface variability mapped separately in groups defined by sex and handedness. Presented are the (a) overall female sample ($n = 29$), (b) overall male sample ($n = 30$), (c) left-handed females ($n = 14$), (d) left-handed males ($n = 15$), (e) right-handed females ($n = 15$), (f) right-handed males ($n = 15$), (g) overall left-handed sample ($n = 29$), (h) overall right-handed sample ($n = 30$). The color bar encodes the root mean square magnitude (in millimeters) of the displacement vectors required to map equivalent surface points from each individual to the group average. The anterior third is on the left and the splenium on the right.

Table 2			
Correlations of real value asymmetry indices			
	STS	PSA	SFP
STS	1.000	—	—
PSA	0.406**	1.000	—
SFP	0.488**	0.526**	1.000

**Significant correlations with a two-tailed probability value of 0.01 (STS = superior temporal sulcus ascending branch posterior extrema, PSA = post central sulcus anterior extrema, SFP = Sylvian fissure posterior extrema).

sulcal measures: (i) the superior temporal sulcus ascending branch posterior extrema, (ii) post central sulcus anterior extrema, and (iii) SF posterior extrema. Relationships between the *real values* of these hemispheric asymmetry measures and callosal areas were thus assessed. All of these variables were significantly correlated (Table 2), and therefore considered as a single hypothesis test. Corrections for multiple comparisons were thus not applied.

Statistical tests assessing the relationships between callosal areas and these sulcal asymmetry measures revealed that when the asymmetry was biased, increased asymmetries predicted

Table 3

Summary of significant correlations between real value sulcal asymmetry coefficients and callosal areas

Region	Total <i>n</i> (<i>n</i> = 59)	Males (<i>n</i> = 30)	Females (<i>n</i> = 29)	Left-handed (<i>n</i> = 29)	Right-handed (<i>n</i> = 30)
Sylvian fissure posterior extrema (SFP)					
Total area	-0.288 ^a	—	—	—	-0.399 ^a
Anterior third	-0.314 ^a	—	—	—	-0.444 ^a
Post central sulcus anterior extrema (PSA)					
Splenium	—	0.361 ^{a,b}	—	0.370 ^{a,b}	—

^aSignificant correlations with a two-tailed probability value of 0.05.

^bNegative *r*-values reflect associations between increased callosal areas and increased leftward asymmetries.

^cPositive *r*-values reflect associations between increased callosal areas and decreased leftward asymmetries.

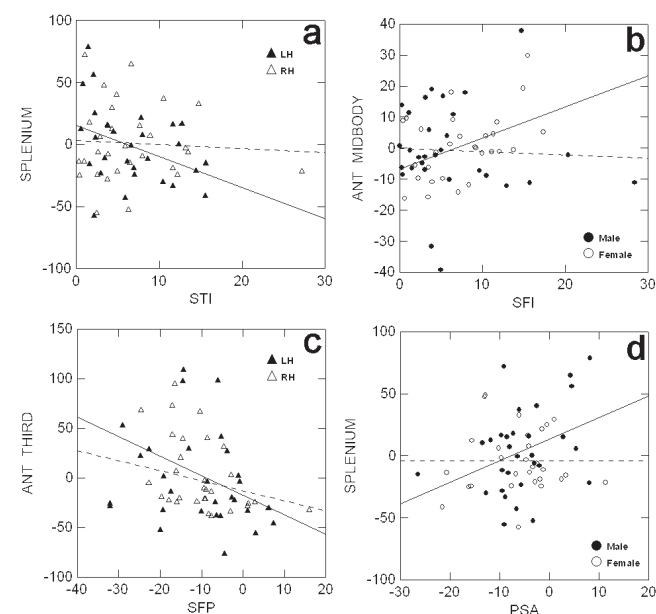


Figure 5. Relationships between real and absolute sulcal asymmetry measures and callosal size. Examples of correlations between absolute (*a, b*) and real (*c, d*) values of sulcal asymmetries (plotted on the *x*-axes in mm) and callosal regions (plotted on the *y*-axes in mm²). (*a*) Relationships between splenium and sulcus triangularis inferior extrema (STI) in left-handers (LH). (*b*) Relationships between anterior midbody and Sylvian fissure inferior extrema of the anterior horizontal ramus (SFI) in females. (*c*) Relationships between anterior third and Sylvian fissure posterior extrema (SFP) in right-handers (RH). (*d*) Relationships between splenium and post central sulcus anterior extrema (PSA) in males. The solid line marks the significant correlation, the dotted line the non-significant correlation.

larger areas of the midsagittal CC. These relationships were significant for the SF posterior extrema and total callosal area, and for the SF posterior extrema and the CC anterior third (for the whole sample and in right-handers). The inverse relationship, however, also appeared true for some highly asymmetric sulcal measures. That is, greater asymmetry bias and decreases in CC areas were revealed for the post central sulcus anterior extrema and the splenium in males and in left-handers (Table 3, Fig. 5).

Measures indicating no significant sulcal asymmetry shift in any direction from exact binomial modeling were found for the (i) SF superior extrema, (ii) sulcus triangularis inferior extrema, (iii) SF anterior extrema of the anterior vertical ramus and (iv) SF inferior extrema of the anterior horizontal ramus. For these

Table 4

Correlations of absolute value asymmetry indices

	SFS	SFI	STI	SFA
SFS	1.000	—	—	—
SFI	-0.305*	1.000	—	—
STI	-0.402**	0.650**	1.000	—
SFA	0.049	-0.308*	-0.072	1.000

*Significant correlations with a two-tailed probability value of 0.05

**Significant correlations with a two-tailed probability value of 0.01 (SFS = Sylvian fissure superior extrema, SFI = Sylvian fissure inferior extrema of the anterior horizontal ramus, STI = sulcus triangularis inferior extrema, SFA = Sylvian fissure anterior extrema of the anterior vertical ramus).

Table 5

Summary of significant correlations between absolute value sulcal asymmetry coefficients and callosal areas

Region	Total <i>n</i> (<i>n</i> = 59)	Males (<i>n</i> = 30)	Females (<i>n</i> = 29)	Left-handed (<i>n</i> = 29)	Right-handed (<i>n</i> = 30)
Sulcus triangularis inferior extrema (STI)					
Splenium	—	—	—	-0.386*	—
Sylvian fissure inferior extrema of the anterior horizontal ramus (SFI)					
Anterior midbody	—	—	0.441*	—	—
Sylvian fissure superior extrema (SFS)					
Anterior midbody	—	—	—	—	0.413*
Isthmus	—	-0.375*	—	—	—
Splenium	—	—	0.368*	—	—

*Significant correlations with a two-tailed probability value of 0.05.

sulcal measures relationships between the *absolute values* of hemispheric asymmetry and callosal areas were assessed. Again, Bonferroni corrections were not employed for these sulcal asymmetry measures given that all asymmetry indices were significantly correlated (Table 4).

In males, a significant negative correlation between SF superior extrema asymmetry and callosal isthmus was observed. There was also a significant negative correlation between the asymmetry of the sulcus triangularis inferior extrema and splenium in left-handers. In contrast, a positive correlation was found between the asymmetry index of the SF inferior extrema of the anterior horizontal ramus and the anterior midbody in females. Additionally, we observed positive correlations between SF superior extrema asymmetry and anterior midbody in right-handers, and splenium in females (Table 5).

Discussion

Gender Effects on Corpus Callosum Morphology

Significant differences were not observed in comparisons of callosal areas between groups defined by biological sex. These results are consistent with a number of studies that have failed to replicate some early findings of gender specific differences in callosal morphology. As argued by Bishop and Wahlstein (Bishop and Wahlstein, 1997) based on their review of 49 independent studies on the human CC from 1982 to 1994, there is insufficient evidence to support the presence of sex-related differences in the size or shape of the splenium, whether or not adjustments are made for overall brain size. Similarly, our results suggest that the effect of individual variation in callosal size is large enough to outweigh any effect of callosal size differences between males and females.

The gender-specific maps of callosal surface anatomy (Fig. 3) demonstrate, however, after correcting for brain size by transforming image volumes into average stereotaxic 305 space, that

small differences between male and female CC are present and are predominantly situated in anterior and posterior callosal regions. These differences might be the result of a somewhat longer CC in females, although this hypothesis was not examined empirically. Maps of callosal surface anatomy may also suggest a slightly more bulbous splenial region in females that might agree with the reported, although controversial, sexual dimorphism of a more bulbous splenium in females (DeLacoste-Utamsing and Holloway, 1982; Holloway and DeLacoste, 1986; Clarke *et al.*, 1989; Allen *et al.*, 1991). This difference, however, was not determined as significant in our analysis of splenial length between groups defined by biological sex.

Handedness Effects on Corpus Callosum Morphology

Statistical analyses comparing individuals based on hand preference did not yield any significant differences for all callosal measures before or after brain size correction. These results are in contrast to some post-mortem findings by Witelson (Witelson, 1985, 1989) demonstrating that the CC of non-consistent right-handed males tend to be thicker than those of consistent right-handed males. A more recent study replicated these findings (Witelson and Goldsmith, 1991) and results from some *in vivo* investigations add further support to these findings (Denenberg *et al.*, 1991; Habib *et al.*, 1991). Notwithstanding, in line with our results, several other MRI studies have failed to detect differences in callosal morphology in relation to handedness (Kertesz *et al.*, 1987; Steinmetz *et al.*, 1992, 1995).

Maps of average callosal surface anatomy in right and left handers (Fig. 3) suggest that diversity exists in the shape of the splenium, but differences were not observed statistically. Nevertheless, given that splenial shape differences have also been implicated previously between males and females, a more refined measure of splenial shape (in addition to splenial length) may be necessary to finally resolve the presence of both gender and handedness differences in splenial morphology.

Sulcal Asymmetries and Callosal Size

Our study demonstrates that both positive and negative associations exist between sulcal asymmetries in the human brain and callosal area measures. As demonstrated by Aboitiz *et al.* (Aboitiz *et al.*, 1992a), an increased callosal area indicates an increase in the total number of fibers crossing the CC. Therefore, our findings support the hypothesis that increased asymmetry is associated with increased callosal connectivity, but also support the inverse relationship showing increased asymmetry is associated with decreased callosal connectivity. Importantly, the direction of these relationships appear influenced by the respective local indicators of cerebral asymmetry suggesting that callosal fibers, whether through their primary or secondary connections with different cortical regions, subserve different functions. These findings further suggest that relationships between cerebral asymmetry and callosal size are local in nature. The region-specific direction of associations between cerebral asymmetry and callosal size seems to be plausible given that the degree of structural asymmetry has been hypothesized to be linked with the degree of functional lateralization, and given that different brain functions subserved by different brain regions are processed through different callosal channels and in different ways (e.g. the non-dominant processing hemisphere might or might not receive information from the dominant processing hemisphere). Our data therefore show that it is an oversimplification to assume a general (inversed) relationship between cerebral asymmetry and callosal connectivity.

Previous anatomic studies support that different cortical

regions project through specific callosal channels (DeLacoste *et al.*, 1985). Interestingly, in addition to significant correlations supporting the assumption that cortical areas are topographically mapped in the CC, we also observed correlations between posterior callosal regions and anterior cortical asymmetries (e.g. between callosal splenium and sulcus triangularis inferior extrema) and, vice versa, between anterior callosal regions and posterior cortical asymmetries (e.g. between callosal anterior third and SF posterior extrema). Although these findings are not immediately understandable, they might lead to the assumption that the nature of callosal pathways is probably much more complex than pictured in present models of inter-hemispheric communication. Existing findings have already suggested that callosal connectivity is more complex than initially assumed. For example, it has been documented, that primary and secondary somatosensory, auditory, and visual information is transmitted via large diameter callosal fibers, while higher-order sensory and cognitive information is transmitted through small diameter fibers (Aboitiz *et al.*, 1992a). Although connections across the corpus callosum have been shown to be topographically organized where the relay of sensory, motor and cognitive information are transmitted from largely homologous regions in the two cerebral hemispheres, there are differential representations of large and small diameter fibers in different callosal channels (Aboitiz *et al.*, 1992a). Anterior callosal regions (connecting frontal brain regions) may be more involved in the transmission of cognitive information, and some middle and posterior connections appear more involved in transmitting sensory information (Clarke *et al.*, 1998). The isthmus, however, has been demonstrated to connect myelinated fibers from posterior language regions and auditory association areas, and has shown links with the performance for the interhemispheric transfer of auditory stimuli as well as semantic-verbal information that may also reflect processing capabilities in anterior language regions (Clarke and Zaidel, 1994).

The present results further demonstrate that the direction of the correlations between sulcal asymmetry and callosal measurements are sensitive to variations in the methods (e.g. whether real or absolute asymmetry values are examined, or whether brain size corrections are employed). Finally, individual differences including sex and handedness are shown to be important when determining the direction, magnitude and significance of correlations between sulcal asymmetry measures and midsagittal callosal size.

Negative Relationships and Absolute Asymmetry Measures

Negative correlations suggest that increased asymmetries in frontal and temporo-parietal regions are associated with decreased callosal size. In our study, negative relationships between the *absolute* asymmetry values of sulcus triangularis inferior extrema and the splenium in left handers, as well as between SF superior extrema and isthmus in males were demonstrated. These results agree with the *in vivo* findings of Dorion *et al.* (Dorion *et al.*, 2000), the post-mortem-results of Aboitiz *et al.* (Aboitiz *et al.*, 1992b,c) and Zaidel *et al.* (Zaidel *et al.*, 1995) in the human brain, as well as with the findings of Rosen *et al.* examining asymmetries in rat cortices (Rosen *et al.*, 1989, 1990).

A number of additional post-mortem (Witelson, 1985, 1989; Witelson and Goldsmith, 1991) and *in vivo* studies (Denenberg *et al.*, 1991; Habib *et al.*, 1991; Hines *et al.*, 1992) assessing relationships between callosal size and hand preference also suggest that right-handed individuals, who are presumably more

lateralized, have smaller callosal size than non-consistent right-handed individuals. If we agree with the hypothesis that anatomical asymmetry is the substrate of the functional lateralization and callosal size reflects callosal connectivity, these findings suggest, that increased hemispheric asymmetry occurs with decreased callosal connectivity as already proposed by Rosen *et al.* (Rosen *et al.*, 1989, 1990) and Galaburda *et al.* (Galaburda *et al.*, 1990). This assumption is consistent with the findings of negative correlations between sulcal asymmetry measures and CC areas observed in our study as mentioned above. Negative correlations between callosal size and cerebral asymmetry might be due to a decreased interhemispheric information exchange with increasing cerebral asymmetry. Based on the assumption that the degree of structural asymmetry is related to the degree of functional lateralization, increased hemispheric independence/dominance may result in less inter-hemispheric communication.

Positive Relationships and Absolute Asymmetry Measures

Importantly, in addition to findings supporting inverse relationships between the magnitude of sulcal asymmetry measures and callosal size, we found evidence to support that the opposite relationship also applies for some sulcal asymmetry measures. Positive correlations were observed between *absolute* asymmetry values of the SF inferior extrema of the anterior horizontal ramus and the anterior midbody in female subjects, and between SF superior extrema and anterior midbody in right handers, and the splenium in females (Table 5). These findings might suggest, in contrast to some previous reports, that increases in the magnitude of cerebral asymmetries are associated with more, rather than less callosal connectivity. Positive correlations between callosal size and cerebral asymmetry might be due to an increased need of interhemispheric communication with increasing cerebral asymmetry in order to relay results from the dominant processing hemisphere to the non-dominant hemisphere. On the other hand, it might also be assumed, that an increase in callosal size is related to an increase of inter-hemispheric inhibition. Thus, positive correlations between callosal size and cerebral asymmetry may arise from a decreased interhemispheric information exchange with increasing asymmetry. This assumption agrees with former theories understanding callosal size as an indicator for hemispheric isolation (Clarke *et al.*, 1993; Clarke and Zaidel, 1994; Hellige *et al.*, 1998), or indicative for 'homotopic inhibition' as described by Cook (1984a,b,c).

Real Asymmetry Measures

Results revealed that if the asymmetry of the SF posterior extrema is shifted leftward (typical shift), then the brains showing the greatest shift exhibit larger overall areas of the CC and of the CC anterior third. In contrast, brains with the most extreme asymmetry of the post central sulcus anterior extrema in the typical shifted direction (leftward), tend to have the smallest spleniums. Therefore these results suggest that the direction of cerebral asymmetries (typical vs atypical) influences the relationships between sulcal asymmetries and callosal size.

Effects of Sex and Handedness on Relationships Between Sulcal Asymmetries and Callosal Size

In this study, a positive relationship between the asymmetry index of the SF inferior extrema of the anterior horizontal ramus and the CC anterior midbody, and between SF superior extrema and splenium was observed in females. In contrast, a significant

negative relationship was observed between the post central sulcus anterior extrema and the splenium in males if the asymmetry was biased in the typical direction (leftward). In addition, we found a significant negative correlation between the asymmetry index of the SF superior extrema and isthmus in males. The latter finding agrees with those of Aboitiz *et al.* (Aboitiz *et al.*, 1992b,c) and Zaidel *et al.* (Zaidel *et al.*, 1995). Using post-mortem brains, investigators observed a negative correlation between perisylvian asymmetries and isthmal area or the total numbers of fibers in the isthmus, in males. Our findings together with those of Dorion *et al.* (Dorion *et al.*, 2000), Aboitiz *et al.* (Aboitiz *et al.*, 1992b,c) and Zaidel (Zaidel, 1995) support that sexually dimorphic processes in the brain might influence the relationships between cerebral asymmetries and callosal connectivity (Zaidel *et al.*, 1995; Wisniewski, 1998). Nevertheless, it may be too speculative to relate our results in detail to interpretations of gender-specific brain organization with regard to our findings of different correlations between sulcal and callosal measures in men and women. However, several studies have documented that male brains may be more lateralized in function (Shaywitz *et al.*, 1995; Hiscock *et al.*, 2001) or asymmetric in structure (Jancke *et al.*, 1994; Kulynych *et al.*, 1994; Amunts *et al.*, 2000) than female brains. Furthermore, on average, men appear to possess better spatial and mathematical abilities while women possess better verbal abilities (Kimura, 1999). Sex dependent relationships with respect to the SF inferior extrema, which borders anterior language regions (Broca's), and the anterior midbody of the corpus callosum, connecting primarily frontal brain regions, may thus reflect differences in the requirements for interhemispheric communication between males and females. It is possible that females, if less functionally asymmetric, may rely on increased interhemispheric communication and thus exhibit stronger relationships between structural asymmetries and callosal size in anterior callosal regions transmitting language related information.

Our finding of correlations in female subjects, results not observed previously, might reflect differences in methods with regard to including brain size corrections. Brain size contributes to increases in cortical asymmetry, where the magnitudes of left-right differences are greater in larger brains. Differences in brain size between males and females may therefore have implications for gender differences in cerebral asymmetries. Similarly, relationships exist between callosal size and brain size (Rauch and Jenkins, 1994; Jancke *et al.*, 1997). Brain size corrections are therefore clearly necessary to accurately establish the direction and magnitude of relationships between structural asymmetry measures and CC size. In addition, relationships between cerebral asymmetries and callosal variables appear dependent on the asymmetry measures used for assessment (area, volume, sulcal extreme, slope, length, height, etc.). This assumption may partially explain why previous studies found only negative relationships between callosal size and hemispheric asymmetry measures while we found both positive and negative relationships to exist when using seven different sulcal asymmetry measures from brain regions established as important for language processing. Other possible explanations for discrepancies in results regarding the direction of these relationships may be attributable to measuring fiber density as oppose to callosal area. As visualized in Figure 5, an additional gain of information is revealed by using *real* left minus right asymmetry measures in contrast to *absolute* value asymmetry indices, as statements regarding whether leftward or

rightward asymmetry has an influence on the direction of the correlation may be interpreted.

Hand preference in addition to biological sex appeared to influence the direction and magnitude of relationships between sulcal asymmetry measures and callosal areas. Positive relationships between the SF superior extrema and anterior midbody in right handers were exhibited, as well as between the SF posterior extrema, total callosal area, and the CC anterior third in right handers if the asymmetry was biased in the typical direction (leftward). In contrast, we observed a negative correlation between the sulcus triangularis inferior extrema and splenium in left handers. An additional negative relationship was detected between the post central sulcus anterior extrema and the splenium in left handers if the asymmetry was biased in the typical direction (leftward). Significant associations between asymmetry measures and anterior callosal regions (anterior midbody, anterior third) were therefore more prominent in right handers while significant correlations with posterior callosal regions (splenium) were apparent in left handers. These results may suggest a dimorphic organization in the brains of left and right handers influencing regionally specific relationships between surface asymmetries and callosal connectivity.

Notes

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